REMARKS/ARGUMENTS

The present application was the subject of an Office Action mailed on October 29, 2008. Claims 46-49, 51-53, 56-64, 72-80, 82-89 and 189-193, 195-201, and 203-215 were rejected. In this response, claims 56 and 64 have been cancelled, and new claims 216-217 have been added. The pending claims therefore are 46-49, 51-53, 57-63, 72-80, 82-89, 189-193, 195-201, and 203-217.

The claims stand rejected under §103(a) as unpatentable over Hoffman (US 2002/0165146), taken alone or in combination with Skrabanja (US 5,929,028). Applicant submits, however, that the claims are patentable over these references for reasons set forth herein.

The State of the Art and Ordinary Skill at the Time of Making the Invention

To understand the present invention in a proper perspective, it is necessary to consider the state of the art at the time the invention was made. Previously, the prior art generally relied upon freeze-dried preparations in order to achieve the necessary level of stability and potency for FSH treatments. These freeze-dried preparations had to be reconstituted each time a dose was required – over and over again, day after day. Since FSH treatments typically require administration of FSH over several days, the burden of repeated reconstitutions of dried preparations was considerable. There was therefore a substantial need for a liquid FSH formulation that could be used over a period of days.

The long-existing need for a liquid FSH formulation which was stable and preserved for use over an extended period of time is reflected in the introductory portion of the Skrabanja publication:

> "The stability of proteins in aqueous formulations is generally a problem in [sic] pharmaceutical industry. Likewise the stability of aqueous solutions of the gonadotropins is insufficient to allow storage for longer times. This is especially true for preparations containing the very pure gonadotropins, prepared using recombinant DNA methods, in relatively dilute solutions." Skrabanja, column 2, lines 21-27.

The existence of this long felt need is further evidenced by the long standing (30+ years) sale of FSH formulations in the onerous form of a lyophilized powder requiring daily reconstitution for as many as 14 consecutive days. The present invention solves that need by providing a liquid formulation that is both preserved and stable, and therefore is a multi-use medication.

The cited Hoffman reference focuses on FSH formulations using particular preservatives. This addresses one requirement for a multi-use product – the inclusion of a preservative. However, a practical product requires more – including a stabilizer to prevent the FSH from degrading over time. The same basic problem presented to Hoffman in identifying useable preservatives remained thereafter with respect to the selection of useable stabilizers and other excipients – the inate instability of the fragile FSH dimer. Thus, while Hoffman lists a number of potential ingredients for its FSH formulations, including solubilizers and surfactants, it does nothing to resolve the issue of selecting a number of specific ingredients which are mutually-compatible and which do not adversely impact the stability of the FSH.

The Present Inventions

The present application solves the problem of providing stable, multi-use, liquid FSH formulations. All of the pending claims cover formulations which include FSH, m-cresol or phenol, poloxamer 188, and a diluent, and which have "a stability sufficient to avoid precipitation." Some claims further limit the nature of the FSH to recombinant FSH; others call for the additional presence of sucrose, methionine, and/or a buffer. Some of the claimed

formulations also include LH. Still other claims provide formulations which "consist essentially of" the foregoing constituents. These different types of claims are discussed separately hereafter.

First, however, Applicant wishes to correct the characterization of the claims contained in section 3 of the Office Action (page 3, lines 1-2) and section 4 of the Office Action (page 6, lines 18-19). The pending claims do not encompass any one of poloxamer 188, poloxamer 217, poloxamer 237 or poloxamer 238, but instead only relate to poloxamer 188. Also, the claims are not limited to m-cresol, but rather encompass m-cresol and/or phenol.

A particular advantage of the present invention is that the formulations provide stable and preserved products of FSH (with or without LH). The formulations are an elegant combination of components which meet the requirements for multi-use applications. As indicated, FSH is generally administered in a regimen of several days, and it is therefore desirable to have a liquid solution which can be used over that time period. Such formulations are referred to in the present application as "multi-dose use" or "multi-use" (citations herein are to the published application US 2006/0147480):

> "The expression 'multi-dose use' is intended to include the use of a single vial, ampoule or cartridge of an FSH formulation or a formulation of FSH and LH for more than one injection, for example 2, 3, 4, 5, 6 or more injections. The injections are preferably made over a period of at least at or about 12 hours, 24 hours, 48 hours, etc., preferably up to a period of at or about 12 days. The injections may be spaced in time, for example, by a period of 6, 12, 24, 48 or 72 hours." '480, [0055]

To be useful in this manner, the formulations must be stable, bacteria-free, and viable for the length of the regimen. The claimed formulations comprise an efficient array of constituents to satisfy the various requirements for multi-use formulations.

FSH

The FSH itself is described in detail in the specification. Preferably, recombinant FSH is used. However, this presents additional difficulties as the more pure FSH materials have been known to be even less stable in solution, particularly in the presence of other constituents. The present invention nevertheless is able to provide liquid formulations - even of recombinant FSH - which have the required stability and potency.

The sustained efficacy, or "potency", of the FSH over multiple uses is described in the specification as follows:

> "The term 'potency' in relation to FSH activity, refers to the ability of an FSH formulation or a mixed formulation, to elicit biological responses associated with FSH, such as ovarian weight gain in the Steelman -Pohley assay, or follicular growth in a female patient. Follicular growth in a female patient can be evaluated by ultrasound, for example, in terms of the number of follicles having a mean diameter of at or about 16 mm on day 8 of stimulation. Biological activity is evaluated with respect to an accepted standard for FSH.
>
> The term 'potency' in relation to LH activity, refers to the ability of an LH formulation or a mixed formulation, to elicit biological responses associated with LH, such as seminal vesicle weight gain method. Biological activity of LH is evaluated with respect to an accepted standard for LH." '480, [0044-0045]

Multi-Use

To be available for multi-day use, the inventive formulations must not allow unacceptable bacterial growth over that time period. A bacteriostatic agent, namely m-cresol and/or phenol, is used. As indicated in the specification:

> "The term 'bacteriostatic' or 'bacteriostatic agent' refers to a compound or compositions added to a formulation to act as an anti-bacterial agent. A preserved FSH or FSH variant or FSH and LH containing formulation of the present invention preferably meets statutory or regulatory guidelines for preservative effectiveness to be a commercially viable multi-use product, preferably in humans. Examples of bacteriostatics include phenol, m-cresol . . . ." (Emphasis added.) '480, [0048]

Stabilizer

Stability is also key in order for the FSH to retain sufficient efficacy for several days. Instability can result from chemical degradation, aggregation, dissociation and several other causes of structural modifications:

> "The term 'stability' refers to the physical, chemical, and conformational stability of FSH and LH in the formulations of the present invention (including maintenance of biological potency). Instability of a protein formulation may be caused by chemical degradation or aggregation of the protein molecules to form higher order polymers, by dissociation of the heterodimers into monomers, deglycosylation, modification of glycosylation, oxidation (particularly of the a-subunit) or any other structural modification that reduces at least one biological activity of an FSH polypeptide included in the present invention.
>
> A 'stable' solution or formulation, is one wherein the degree of degradation, modification, aggregation, loss of biological activity and the like, of proteins therein is acceptably controlled, and does not increase unacceptably with time. Preferably the formulation retains at least at or about 80% of the labelled FSH activity and at least at or about 80% of the labelled LH activity over a period of 6 months at a temperature of at or about 2-8°C, more preferably at or about 2-8°C, more preferably at or about 4-5°C. FSH activity can be measured using the Steelman -Pohley ovarian weight gain bioassays. LH activity can be measured using the seminal vesicle weight gain bioassay." (Emphasis added.) '480, [0052-0053]

Achieving such stability in a liquid formulation is extremely difficult. The art taught that formulations of proteins, particularly heterodimeric proteins such as FSH, are susceptible to numerous avenues of degradation. References in the prior art confirmed the difficulty of preparing stable protein formulations of FSH or the like, including both of the cited references Hoffman and Skrabanja. In the face of this understanding, the preparation of stable, liquid formulations of FSH remained a long-standing problem.

The problems with formulating FSH solutions include two diverse problems. At low concentrations, there is the potential for FSH to dissociate. At high concentrations, FSH tends to

aggregate. Either of these pathways can render the FSH ineffective. In addition, the presence of other constituents, including organic solvents such as m-cresol, can be particularly destabilizing.

The present invention is based in part on the surprising discovery that a preserved and stable FSH solution is obtained when FSH is combined with the specific combination of (1) the bacteriostat(s) m-cresol and/or phenol, and (2) with the stabilizer/surfactant poloxamer 188. The use of poloxamer 188, in contrast to other surfactants, addresses instability whether due to surface adsorption or aggregation/precipitation of FSH:

> "The inventors have found that by formulating FSH and mixtures of FSH and LH with a surfactant selected from block copolymers of ethylene oxide and propylene oxide, . . . particularly preferably Pluronic F68 (BASF, Pluronic F68 is also known as Poloxamer 188) they obtain stable formulations that minimize the loss of active principle (FSH or FSH and LH) caused by adsorption on the surfaces of the vial and/or delivery device (e.g., syringe, pump, catheter, etc.). '480, [0057]

By comparison, the use of the common stabilizer Tween 20 results in unstable solutions:

> The inventors have further found that by formulating FSH and mixtures of FSH and LH with a surfactant selected from block copolymers of ethylene oxide and propylene oxide, . . . particularly preferably Pluronic F68 (BASF, Pluronic F68 is also known as Poloxamer 188) they obtain a stable formulation that avoids the problem of precipitation in the presence of a bacteriostatic agent, such as m-cresol and phenol. Precipitation, resulting in the formation of turbid or milky solutions occurs when TWEEN 20 is used with m-cresol or phenol." (Emphasis added.) '480, [0058].

Liquid Solution

The inventive FSH solutions further comprise a diluent. The primary requirement is that the diluent not contain anything that would interfere with the efficacy or stability of the other indicated components –FSH, the bacteriostat, and the stabilizer. As stated in the specification:

> "The term "aqueous diluent" refers to a liquid solvent that contains water. Aqueous solvent systems may be consist solely of water, or may consist of water plus one or more miscible solvents, and may contain dissolved solutes such as sugars, buffers, salts or other excipients." '480, [0046]

The present invention thereby presents a unique combination of constituents which addresses preservation, stability and potency for multi-use FSH preparations.

Claims 46-49, 51-53, 57-60, 63, 198-201, 203-211
Rejected Over Hoffman Under 103(a)

The identified claims feature the four primary components comprising the present invention, namely, FSH, the bacteriostat(s) m-cresol and/or phenol, poloxamer 188, and the diluent. The invention differs from the prior art in specifically identifying this particularly advantageous combination of components.

Hoffman US 2002/0165146

Hoffman has been cited as teaching formulations of FSH including cresol or phenol. The Hoffman application has also been cited as indicating that other additives such as Tween 20, Pluronic F68, poloxamer 184, or poloxamer 188 can be added to reduce aggregation. However, Applicant submits that reliance on Hoffman, and on a hindsight selection of a few components out of the many listed in Hoffman, is not supported by the art of record. It is inappropriate to point to Hoffman and suggest that it teaches the use of any of a long list of possible excipients, when Hoffman stands for the proposition that the selection of excipients, e.g., the specific preservatives claimed in Hoffman, is not predictable and in fact can form the basis for patentability.

The Hoffman application does not recite only a few potential excipients. It instead provides a long, laundry list of a broad range of possible constituents, including preservatives, isotonicity agents, buffers, antioxidants, and preservative enhancers. Contrary to this lengthy listing is the fact that Hoffman itself recognizes the difficulties of preparing stable protein formulations. Hoffman cites the non-covalent bonding of the FSH subunits as a basis for the

FSH to be "more susceptible to protein destabilizing agents," and Hoffman cites to a number of efforts to "counteract the instability of FSH." Hoffman, [0006, 0010-0011].

The examples in Hoffman do not even include formulations which contain excipients other than preservatives and buffers. No formulations are exemplified in Hoffman which include the myriad other possible constituents named in Hoffman. In a similar vein, Skrabanja also notes the pervasive problem in attempting to prepare preserved, stable, potent, liquid FSH formulations. See, e.g., column 2, lines 21-27. In the face of these teachings of the cited art, and given the level of skill in the art, it must be concluded that a person of ordinary skill in the art would not understand Hoffman as teaching the viability of each of the vast number of combinations of constituents which could be theorized from the Hoffman disclosure. When the elements of a claim are disclosed only in a laundry list of other elements, there is a question whether the reference reasonably teaches a person of ordinary skill in the art to make appropriate selections from the list *without undue experimentation*. Impax Labs v. Aventis Pharms., 545 F.3d 1312 (Fed. Cir. 2008) (citing *FinisarCorp. v. DirecTV Group, Inc.,* 523 F.3d 1323, 1336 (Fed. Cir. 2008).

The present situation is different than where a combination of elements does not present compatibility issues. In some settings, it may be proper to infer that any of a list of possible constituents could be readily, and arbitrarily, selected. However, liquid formulations of FSH were long known before the present invention to be fraught with problems because the highly-sensitive FSH dimeric molecule does not easily formulate with other constituents. That is why patients struggled with reconstituting freeze-dried FSH for 30+ years. The evidence in the record is that the prior art – e.g., Hoffman and Skrabanja – taught that FSH is readily destabilized in the presence of other constituents. In this light, it would require undue experimentation to

develop the formulations of the present invention based on the teachings of the Hoffman reference.

The question of whether experimentation that would be required is "undue" depends on several factors. These factors were enumerated in *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), and include the following:

- The nature of the invention;
- The state of the prior art;
- The level of one of ordinary skill;
- The level of predictability in the art;
- The amount of direction provided by the inventor;
- The existence of working examples; and
- The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

All of these factors should be considered in evaluating the prior art. MPEP 2164.01(a). In the present case, it has been shown that many or all of these factors weight against a teaching of the present invention in the prior art. The art was struggling to solve a long-standing problem of FSH stability, and it considered that formulating FSH solutions was extremely difficult.

The difficulty and unpredictability of preparing FSH formulations is demonstrated by the cited references. The first solubilizer listed in Hoffman is Tween 20, which Skrabanja identified as being "especially preferred." But Tween 20 is unsuitable when used with m-cresol or phenol as it results in a "turbid or milky solution":

> "From visual examination of the formulations, it was determined that TWEEN 20 cannot be used with m-cresol and phenol because FSH formulations containing TWEEN 20 and m-cresol or TWEEN 20 and phenol presented a white opalescent

suspension. In contrast, FSH formulations containing Pluronic F68 did not exhibit this problem with m-cresol and phenol. The use of Pluronic F68 permits the use of phenol and m-cresol." '480, [0195]

Applicant therefore submits that the liquid FSH formulations comprising m-cresol or phenol in combination with poloxamer 188 are unobvious over Hoffman, and that claims 46-49, 51-53, 57-60, 198-201, and 203-211 are therefore patentable over the cited art.

Claim 61 Rejected Over Hoffman Under 103(a)
and New Claim 216

Claims 61 and 216 cover FSH formulations which further include sucrose, methionine and a buffer. Each of these components has a role in assuring that the formulations are preserved, stable and efficacious:

Isotonicity

> "An "isotonicity agent" is a compound that is physiologically tolerated and imparts a suitable tonicity to a formulation to prevent the net flow of water across cell membranes that are in contact with the formulation. Suitable isotonicity agents include, . . . sucrose . . . ." (Emphasis added.) '480, [0047]

Antioxidant

> "Preferably the formulations of the invention contain an antioxidant, such as methionine . . . . The antioxidant prevents oxidation of FSH and LH (particularly the α-subunit)." (Emphasis added.) '480, [0165]

Stabilizer

> Preferably the formulations of the invention contain a mono- or disaccharide or a sugar alcohol as stabiliser and tonicity adjusting agent, such as sucrose . . . . Most preferred is sucrose, preferably at a concentration of at or about 60 mg/ml." (Emphasis added.) '480, [0167]

Buffer

> "The term 'buffer' or 'physiologically-acceptable buffer' refers to solutions of compounds that are known to be safe for pharmaceutical or veterinary use in formulations and that have the effect of maintaining or controlling the pH of the formulation in the pH range desired for the formulation. Acceptable buffers for controlling pH at a moderately acidic pH to a moderately

basic pH include, but are not limited to, such compounds as phosphate, acetate, citrate, arginine, TRIS, and histidine. "TRIS" refers to 2-amino-2-hydroxymethyl-1,3,-propanediol, and to any pharmacologically acceptable salt thereof. Preferable buffers are phosphate buffers with saline or an acceptable salt." '480, [0049].

Applicant submits that claims 61 and 216 are further distinguished over Hoffman as they require the presence of six separate constituents (in addition to the diluent) – each having an active purpose. Remarkably, the FSH retains its stability and potency in the presence of all of these components.

Claims 212-213 Rejected over Hoffman
Under 103(a) and New Claim 217

Claims 212, 213 and 217 are directed to formulations consisting essentially of FSH, a diluent, m-cresol or phenol, and poloxamer 188, as well as sucrose, methionine, and a buffer. These claims specifically cover FSH formulations that address all requirements for a commercially-viable product. Pharmaceuticals, particularly injectables, must meet stringent requirements for safety and efficacy. The active ingredient, i.e., FSH, must remain biologically active and at an indicated dosage level. Degradation is a particular problem for FSH and it can follow numerous pathways. The practical FSH solution must guard against any such pathway – not just a select one or two pathways - that would render the pharmaceutical unsafe or ineffective. The formulations of claims 212, 213 and 217 include poloxamer 188 to deal, *inter alia*, with adsorption, aggregation and precipitation of the FSH, and include methionine to inhibit oxidation of the FSH. An acceptable pharmaceutical solution must also inhibit bacterial growth, and have suitable tonicity and pH. M-cresol or phenol, sucrose, and a buffer are included in the inventive formulations of claims 212, 213 and 217 to fulfill these three purposes, respectively.

Applicant submits that the subject matter of claims 212, 213 and 217 encompasses basic and novel characteristics in that a pharmaceutical solution of FSH is provided which fulfills all

requirements for safe and effective use, while avoiding the inclusion of excessive numbers of components which could adversely impact stability and potency. These claims are further distinguished from the cited art in this respect, and are therefore submitted to be patentable.

Claims 72-80, 82-85, 88-89, 189-193, 195-197 and 214-215
Rejected over Hoffman in view of Skrabanja Under 103(a)

These claims cover formulations including at least FSH and LH, poloxamer 188, m-cresol or phenol, and a diluent. Applicant submits that these claims are patentable on the same grounds as presented for the similar FSH formulations, *supra*. The presence of the LH only increases the difficulty in formulating a stable, preserved and viable liquid solution of FSH, and adds the further requirement that the LH also remain stable and viable. Applicant submits that the combination of Hoffman and Skrabanja is unavailing on the bases that (1) the references are not combinable, (2) any combination would not yield the present invention, and (3) nothing in the references suggests stability and potency of LH or FSH/LH when combined with the preservatives of Hoffman, and nothing suggests that those preservatives would in fact preserve LH alone or combinations of LH and FSH.

Skrabanja is cited as teaching formulations of FSH and LH. However, Skrabanja, as cited previously, also describes the substantial difficulty in preparing protein solutions. Consequently, Skrabanja does not teach that FSH and LH can successfully be combined with other excipients, except to the extent of the formulations specifically described in Skrabanja.

The Art Would not have Combined the Hoffman and Skrabanja References

The initial premise of the Office Action appears to be that Hoffman "implies" that FSH could be used with other gonadotropins. It is not clear if this is intended to suggest (1) that Hoffman teaches including LH in its own FSH formulations, or (2) that Hoffman teaches that the

LH would be separately administered to a patient. In either case, the result is support for the patentability of the present invention.

It seems evident that Hoffman was not suggesting that LH could be combined in its FSH preparations, and that a person skilled in the art and reading Hoffman would understand it that way. Surely, if Hoffman et al. intended to disclose formulations including FSH and LH, then they would have done so explicitly. Hoffman mentions luteinising hormone (LH), as well as thyroid stimulating hormone and chorionic gonadotropin, as fellow members, along with FSH, of the heterodimer, glycoprotein hormone family. Hoffman, [0006]. Hoffman also lists a large number of potential excipients. Hoffman, [0098-0100]. However, there is no mention of an FSH formulation including another "active ingredient" such as LH. A person skilled in the art would understand the text at paragraph [0028] of Hoffman to indicate that any other gonadotropin there referenced would be administered separately from the FSH, as was a common practice at the time.

If then it is contended that Hoffman suggested that FSH would be administered along with LH, but in separate carriers, then that is even more telling. Applicant acknowledges that Skrabanja describes the use of mixtures of FSH and LH to stimulate the development of ovarian follicles. This practice therefore dates back at least as early as January 15, 1997, the priority date for the Skrabanja patent. However, with this many years of practice in the art, Hoffman makes no suggestion of combining LH into its FSH formulations. And this occurs, despite the fact that LH is specifically mentioned in Hoffman in the prior art section, and as the Office Action notes, is mentioned in Hoffman with respect to use of the described FSH formulations. Hoffman, [0006, 0028]. It is evident that Hoffman did not consider it obvious to prepare its formulations with both FSH and LH, which the Office Action now contends is obvious.

A further position in the Office Action concerning the combination of Hoffman and Skrabanja is that it would have been obvious "to use a combination of FSH and LH because the combination formulation has been used for stimulation of ovarian growth." While true as far as it goes, this statement does not indicate why or how Hoffman and Skrabanja would be combined for this purpose. What would trigger one to locate and combine these two references? The Office Action goes on to say that there "would have been a reasonable expectation of success because the Skrabanja et al. teach [sic] many of the same components in a formulation comprising LH and FSH as taught in Hoffman." In response, Applicant first challenges that some form of "success" would be expected, as argued in more detail hereafter. Second, the Office Action only mentions two such components – sucrose and a "non ionic surfactant such [sic] tween 20 or pluronic f123." These asserted connections of the references are far outweighed by the substantial differences between the two references, also as explained below.

Hoffman deals with a specific issue for FSH formulations, namely, how to inhibit bacterial growth while still having a stable FSH solution. The answer from Hoffman is the use of particular preservatives. Skrabanja on the other hand is also concerned with stability for FSH solutions, but takes a totally different approach. Skrabanja provides a unique stabilizing formula consisting of a polycarboxylic acid, or a salt thereof, and a thioether compound. It is not clear why or how a person skilled in the art would combine these teachings. One reference (Hoffman) relates to the selection of preservatives and the other (Skrabanja) doesn't even mention preservatives. Hoffman mentions aggregation while Skrabanja deals with surface adsorption. Both are concerned with stability of liquid FSH formulations, but they take totally different approaches.

In contending for a 103 combination of references, it is necessary to consider the disclosures as a whole, not just isolated words or phrases. With this perspective, it is clear that one of the greatest connections between Hoffman and Skrabanja is the fact that both acknowledge the lack of "expectation of success" when formulating FSH solutions. When a second heterodimer, LH, is added to the mix, the number of component interactions, and therefore the difficulties, more than double.

It appears at best that the argument against patentability is that it would simply be obvious to drop LH into the Hoffman formulations and that there would be an alleged expectation that a suitable solution would be obtained. The problem with this approach is that there is nothing in either reference to suggest that LH would be stable in the Hoffman formulations, e.g., with the selected preservatives. Indeed, the cited art itself repeatedly emphasizes the difficulty in finding preservatives (and other excipients) that do not degrade gonadotropins. Hoffman indicates, for example, that "preservatives as a class, however, tend to be detrimental to the stability of proteins." Hoffman, [0006]. Hoffman goes on to say that m-cresol "has been reported to generally combine with and denature proteins" and that it "also presents particular difficulty with the solution stability of hormones, such as human growth hormone." Hoffman, [0005]. Thus, the very reference that is being asserted to show the obviousness of a stable, preserved, liquid solution of FSH and LH is in fact one that argued for patentability on the basis that such combinations were unobvious and taught against in the art. Also as already noted, it is telling that Hoffman did not make any suggestion to combine LH in its FSH formulations.

By comparison, Skrabanja also provides no teaching or suggestion that LH alone, or LH in combination with FSH, would be stable in the presence of the preservatives discussed in

Hoffman. As mentioned, Skrabanja does not refer to any preservatives for its formulations. More to the point, Skrabanja's answer to the stability issue is quite different – it involves a mix of two different stabilizers.

Applicant therefore submits that a person of ordinary skill in the art would not combine the Hoffman and Skrabanja references.

Combining Hoffman and Skrabanja Does Not Yield the Present Invention

Assuming, *arguendo*, that Hoffman and Skrabanja were to be combined in some manner, Applicant submits that the result would not be the present invention. Again, there is no direction to indicate which ones of the vast number of potential excipients would be involved. Hoffman provides a laundry list, but its examples do not demonstrate their use. To the extent the excipients in Hoffman are cited with respect to stability, the reference is to inhibiting aggregation of the FSH. However, Skrabanja makes no mention of aggregation as a problem for its formulations. There is nothing from which to conclude how a person of skill in the art would choose to combine these different teachings.

Claims 86-87 Rejected over
Hoffman in view of Skrabanja Under 103(a)

Claims 86 and 87 are in parallel with claims 61 and 216 in that they cover FSH formulations which further include sucrose, methionine and a buffer, except that claims 86 and 7 also include LH. Each of the claimed components has a role in assuring that the formulations are preserved, stable and efficacious. Applicant therefore submits that claims 86 and 87 are further distinguished over Hoffman in combination with Skrabanja as the claims require the presence of six separate constituents (in addition to the diluent) – each having an active purpose. Remarkably, the FSH and LH retain their stability and potency in the presence of each other, and in the presence of the other components.

Claim 214 Rejected over
Hoffman in view of Skrabanja Under 103(a)

Claim 214 is directed to formulations consisting essentially of FSH, LH, a diluent, m-cresol or phenol, and poloxamer 188, as well as sucrose, methionine, and a buffer. This claim specifically covers combined FSH and LH formulations that address all requirements for a commercially-viable product. The practical FSH/LH solution must guard against degradation or other effects that would render the pharmaceutical unsafe or ineffective. The formulations of claim 214 include poloxamer 188 to deal, *inter alia*, with adsorption, aggregation and precipitation, and include methionine to inhibit oxidation. M-cresol or phenol, sucrose, and a buffer are included in the inventive formulations of claim 214 to inhibit bacterial growth, and to provide suitable tonicity and pH, respectively.

Applicant submits that the subject matter of claim 214 encompasses basic and novel characteristics in that a pharmaceutical solution including both FSH and LH is provided which fulfills all requirements for safe and effective use, while avoiding the inclusion of excessive numbers of components which could adversely impact stability and potency. This claim is further distinguished from the cited art in this respect, and is therefore submitted to be patentable.

Assuming a combination of the Hoffman and Skrabanja references, Applicant submits that, at least, the resultant would include a polycarboxylic acid or salt thereof, because the teaching from Skrabanja is that when FSH and LH are combined, then a special stabilizer system is required. Claim 214 precludes the presence of a polycarboxylic acid or salt thereof, and therefore is unobvious over the combination of Hoffman and Skrabanja for that additional reason.

rFSH claims 53, 61, 62, 74, 86, 87, 195, 205, 212-217, and others

As stated in Skrabanja, stability problems due to surface adsorption are particularly critical for formulations comprising recombinant FSH in low concentrations. The claimed formulations including rFSH are therefore further distanced from the teachings of Hoffman, which mentions dealing with aggregation concerns. Consequently, claims 53, 61, 62, 86, 87, 195, 205, and 212-215, directed to recombinant FSH, are even more distinguishable from the cited references and are patentable on that additional basis.

Conclusion

It is clear that the state of the art, and the level of skill in the art, at the time the present invention was made was that the preparation of stable FSH formulations was known to be a difficult proposition, with essentially any change or addition as to excipient(s) having the potential of resulting in instability. Applicant submits that exhaustive lists of widely diverse components, as found in Hoffman and Skrabanja, do not direct a person of ordinary skill in the art to select particular combinations of functional components, and do not provide an expectation of success in the selection of such combinations. This is particularly true in the present situation, in view of the state of the art and the level of skill in the art of protein formulating.

"The patentability of a claim to a specific compound or subgenus embraced by a prior art genus should be analyzed no differently than any other claim for purposes of 35 U.S.C. § 103." MPEP 2144.08. The fact that a claimed species or subgenus is encompassed by a prior art genus is not sufficient by itself to establish a *prima facie* case of obviousness. *In re Baird*, 16 F.3d 380, 382, 29 USPQ2d 1550, 1552 (Fed. Cir. 1994).

As the present application points out, the use of poloxamer 188 (Pluronic F68) with m-cresol or phenol solves a problem of precipitation and provides "clear solutions" which are free

of visible particles. '480, [0179] and Table 8. The present application specifically indicates that poloxamer 188 provides "a stable formulation that avoids the problem of precipitation in the presence of a bacteriostatic agent, such as m-cresol and phenol." '480, [0058].

Applicant submits that the present invention is not obvious over the prior art. The primary reference of record is the Hoffman publication, which itself mentions LH in the prior art and proposes that its FSH formulations may be used with other gonadotropin medications, and yet it fails to teach or suggest the addition of LH to its formulations. The proposition that Hoffman can then be considered to make the present invention obvious must be seen in that light as the application of hindsight. It is necessary to consider the fair, overall teachings of a reference in assessing whether it makes a later invention obvious. Here, Hoffman and Skrabanja clearly describe the difficulties of formulating protein solutions to be preserved, stable and viable. It is apparent from the state of the art that a person of ordinary skill would not consider it a simple matter to pick and choose excipients at random and expect a successful result.

Reconsideration of the above-identified patent application, as amended and in view of the foregoing remarks, is respectfully requested. An action on the merits and allowance of the claims is solicited. If the Examiner believes that it would expedite examination of this case, the Examiner is requested to contact the undersigned directly.

Respectfully submitted,

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